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Organometallic Aspects of Fluoroalkylation Reactions with Copper and Nickel

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Abstract: The development of perfluoroalkylation methods has become increasingly important in synthetic chemistry. However, many of the metal-mediated transformations that occur readily with alkyl substrates can proceed slowly, with limited scope, or not proceed at all with fluoroalkyl derivatives. To develop more sophisticated transformations with fluoroalkyl groups using base metals, a better understanding of their fundamental fluoro-organometallic chemistry is needed.

This account describes our recent investigations into the organometallic chemistry of well-defined nickel- and copper-fluoroalkyl complexes, as well as our efforts towards trifluoromethoxylations and trifluoromethylthiolations using those metals. Synthetic routes to the new complexes are discussed, as are their structural and electrochemical properties and chemical reactivities.

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Key words: trifluoromethylation, cross-coupling, nickel, copper, fluorine

1 Introduction

The effective installation of fluoroalkyl groups into organic substrates may ultimately lead to better drugs, pesticides, oils, electronics, gaskets, and seals. Despite the importance of the fluoroalkyl functional group, it remains one of the most challenging moieties to manipulate with transition metal catalysts. For fluoroalkylation methods to evolve with sophistication, it is necessary to understand the fundamental properties of metal-perfluoroalkyl complexes to see how such fluoro-organometallic species can be better coaxed into targeted reactivity patterns. This account describes our recent efforts to prepare and study such well-defined fluoro-organometallic complexes, and focuses on the chemistry of copper and nickel.

Our first entry into the field of fluorine chemistry came somewhat out of necessity rather than from good planning. In 2006, our group's primary area of research was focused on metal-mediated alkylation chemistry, particularly with nickel.^{1–4} We had often thought of testing some

of our catalysts for perfluoroalkylations, but the idea was never taken seriously and resources were not strongly committed to that endeavor.

Then in 2007, our group moved to the University of Hawaii, where there was no functioning gas chromatography/mass spectrometry (GC/MS) equipment in the Chemistry Department; GC/MS was the method by which our group analyzed all of our alkylation reactions. Therefore, for a substantial period of time before the delivery of our own GC/MS equipment to an island in the middle of the Pacific Ocean, our group needed some projects with which we could maintain productivity.

We knew we could potentially analyze fluoroalkylations using ¹⁹F NMR spectroscopy, so we thought we would make a simple evolutionary step in that direction until the infrastructure problems at the University of Hawaii had been resolved. However, little did we know that the move to study fluoroalkylation chemistry would be neither a simple evolutionary step in our research program nor a short-lived undertaking.

2 Bottling a Copper(I)–Trifluoromethyl Source

When we began our studies in fluoroalkylation chemistry, we were well aware of the rich history, dating back to 1969, of using copper to promote stoichiometric perfluoroalkylations.^{5–9} After the initial reports that copper can indeed transfer a perfluoroalkyl group to aryl halides, it became generally regarded that the active species in the cross-coupling reactions was some type of solvated copper(I) species bearing a perfluoroalkyl ligand.

Despite being air sensitive, these copper-perfluoroalkyl reagents were relatively robust, and crude initial evidence for a copper(I) species could be obtained from elemental analysis.⁵ The NMR spectral evidence for a copper-trifluoromethyl species followed in 1986,¹⁰ but Weimers and Burton described solutions of (trifluoromethyl)copper as 'much more complex than previously appreciated.'

After these advances and even into the late 2000s, the (trifluoromethyl)copper species used in synthetic protocols was usually generated in situ for immediate use. For instance, one protocol included flame heating a mixture of potassium fluoride (KF) and colorless copper(I) iodide (CuI) under reduced pressure until a greenish color appeared.¹¹ This resulting green mixture was then added to trimethyl(trifluoromethyl)silane (TMSCF₃) and electron-poor aryl halides in polar solvents, such as *N,N*-dimethyl-

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formamide (DMF) and *N,N*-dimethylacetamide (DMA), to produce trifluoromethylated products.¹¹ Other known protocols to generate an active copper–trifluoromethyl source besides using the CuI/MF/TMSCF₃ system included the use of copper(0)/trifluoro(iodo)methane/hexamethylphosphoramide,^{7,12,13} the transmetalation of copper salts with bis(trifluoromethyl)mercury(II),⁶ the in-situ metathesis of (trifluoromethyl)cadmium and -zinc reagents,¹⁰ and the decarboxylation of sodium trifluoroacetate in the presence of CuI.^{14–16}

With an interest in learning more about how to manipulate the active copper(I)–trifluoromethyl species that was generated in situ, we set out to prepare one that was well defined and isolable. Our motives were to (1) demonstrate that a structurally unambiguous (trifluoromethyl)copper reagent with a long shelf life could be prepared which chemists could bottle and conveniently use, (2) obtain the first full structural parameters of an active copper(I)–trifluoromethyl complex, and (3) produce a complex that would be part of a family of related compounds to facilitate meaningful comparative studies, such as structural and electrochemical ones.

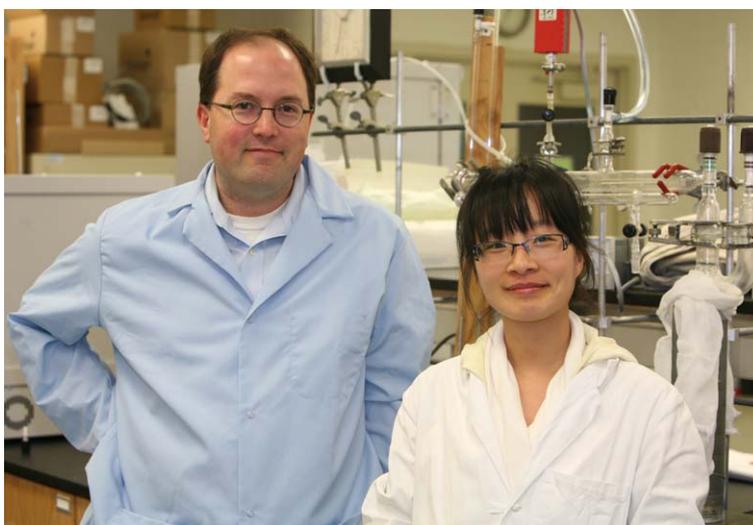
As a starting point, we took inspiration from the ligand frameworks that were present in structurally characterized copper(I)–methyl derivatives. When we began our investigations, we were aware of only five neutral copper(I)–

methyl complexes that were structurally characterized.^{17–21} The derivative that we thought was the easiest to prepare was [(IPr)CuMe] [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene],¹⁸ so we set off to synthesize the fluorinated analogue [(IPr)Cu(CF₃)].

We found that the best way to introduce a trifluoromethyl group (CF₃) to an NHC-ligated (NHC = *N*-heterocyclic carbene) copper complex was to react an NHC-containing copper *tert*-butoxide precursor, such as **1** or **4**, with TMSCF₃ (Schemes 1 and 2).²² We found that when the NHC ligand contained a carbon–carbon double bond, an unexpected silylation occurred in the NHC backbone, e.g. the formation of **3** in greater yield than the desired complex [(IPr)Cu(CF₃)] (**2**) from **1** (Scheme 1).²² Removal of this double bond and the use of saturated NHC ligands provided the clean generation of a copper–trifluoromethyl complex with no silylation of the supporting ligand (e.g., Scheme 2).

Although the copper–trifluoromethyl complexes were air sensitive, both complexes **3** and **5** were stable enough to isolate and structurally characterize. The X-ray data provided the first structural parameters of copper(I)–trifluoromethyl complexes,²² some 39 years after Mcloughlin and Thrower's breakthrough report on copper-mediated perfluoroalkylations.⁵

Biographical Sketches

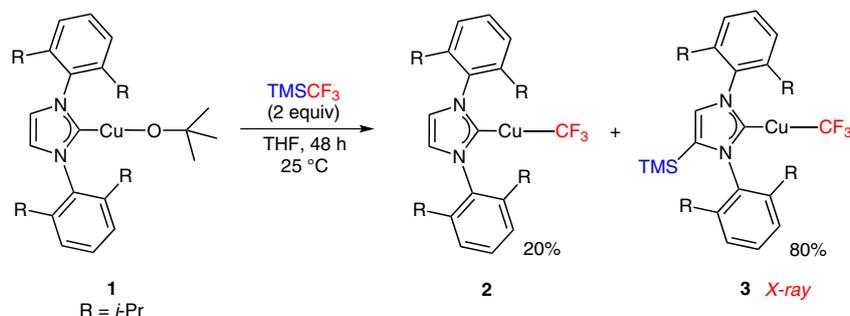


David Vicic was born in the state of Pennsylvania in the USA in 1971. He received a B.A. degree in chemistry from Johns Hopkins University in 1994 and a Ph.D. degree from the University of Rochester in 1999. After an American Cancer Society Postdoctoral Fellowship at the California Institute of Technology, he joined the faculty at the University of Arkansas in 2002. There he was promoted to

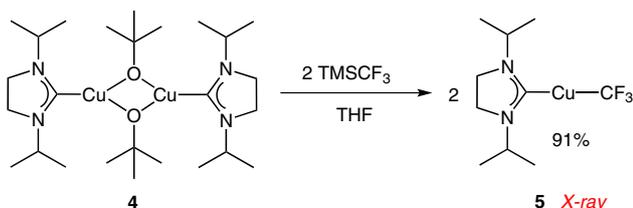
Associate Professor in 2007, and he moved to the University of Hawaii later the same year. In 2012, he returned to his home state to join the faculty at Lehigh University, where he is currently Professor of Chemistry. His research interests lie in the area of organometallic chemistry.

Huan Wang was born in Shandong, P. R. of China, in 1983. She received

a B.A. degree in chemistry from Qufu Normal University in 2007 and a Ph.D. degree from the Shanghai Institute of Organic Chemistry, Chinese Academy of Science, in 2012 after working with Professor Xiyan Lu. She joined the group of Professor David Vicic for postdoctoral studies the same year, where she is working on the fundamental properties of nickel–fluoroalkyl complexes.



Scheme 1



Scheme 2

We were pleasantly surprised to find that the well-defined copper–NHC complexes could also be used as reagents to trifluoromethylate organic halides. One could either use complex **5** directly or use the *tert*-butoxide precursor **4** in the presence of 2 equivalents of TMSCF_3 to trifluoromethylate aryl iodides in high yields at room temperature (Table 1, entries 1–4). The use of homogeneous solutions of these new copper–NHC complexes led, in our hands, to much more reliable results than those obtained using the well-known $\text{CuI}/\text{MF}/\text{TMSCF}_3$ protocol (e.g., Table 1).²²

Having characterized and explored the reactivity of sterically bulky complex **3** and sterically small complex **5**, the intermediate-sized $[(\text{SIMes})\text{Cu}(\text{CF}_3)]$ (**7**, SIMes = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) was prepared by the route described in Scheme 3.²³ In contrast to solutions

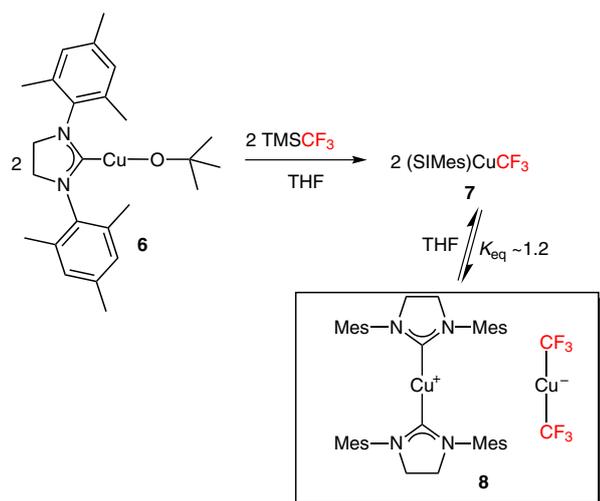
of complexes **3** and **5**, tetrahydrofuran solutions of **7** were found to exhibit two well-separated signals in the ^{19}F NMR spectrum at $\delta -33.0$ and -31.5 (25 °C, $\text{THF}-d_8$). The former signal we attributed to complex **7**.

The species displaying the NMR spectroscopic signal at -31.5 was insoluble in toluene, which permitted its separation. X-ray diffraction studies revealed this new species to be cuprate salt $[(\text{SIMes})_2\text{Cu}][\text{Cu}(\text{CF}_3)_2]$ (**8**) (Scheme 3). The dissolution of crystals of salt **8** in organic solvent verified the equilibrium with **7**, and the equilibrium constant was determined to be 1.2 at 25 °C, slightly favoring the cuprate form.²³ An in situ generated bis(trifluoromethyl)cuprate species had been determined using NMR spectroscopy by two groups before our study,^{10,24,25} but the solubility properties of the NHC-derivatized salt uniquely enabled the separation and the characterization of the cuprate form for the first time.

Studies with neat aryl halides showed that the SIMes ligand afforded the most-active (trifluoromethyl)copper species out of all the NHC ligands tested for activity.²³ It was found that a mixture of **7** and **8** trifluoromethylated phenyl iodide stoichiometrically at room temperature in 4.5 hours to afford (trifluoromethyl)benzene in 99% yield. Even electron-rich 4-bromoanisole could be trifluoro-

Table 1 Trifluoromethylations Mediated by Complex **4** in *N,N*-Dimethylformamide as the Solvent Compared with Results from Using the Copper(I) Iodide and Potassium Fluoride Protocol

Entry	Starting material	Product	Yield (%)	Yield (%) using the CuI/KF protocol
1			94	25
2			91	62
3			99	41
4			99	70
5			58	29



Scheme 3

methylated with **7** and **8**, albeit at an elevated temperature of 85 °C.²³

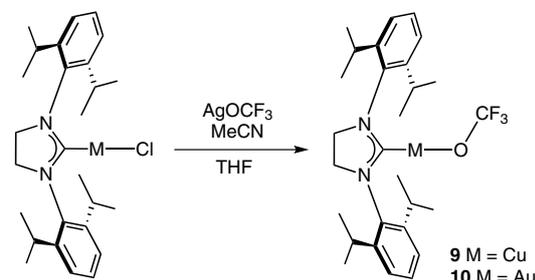
The studies with neat aryl iodides were informative about other aspects. They revealed that the rates of trifluoromethylation by both complex **5** (see Scheme 2) and [(SIMes)₂Cu][Cu(CF₃)₂] (**8**) at 25 °C increase upon decreasing the concentration of the initial copper complex in the range of 0.007–0.029 M. Assuming concentration-dependent equilibria, these data suggest that the neutral form of the complex, and not the cuprate, is the more-active species in the trifluoromethylation reactions. Such a reactivity pattern parallels the observations noted by Buchwald and Hartwig and their co-workers in amidation reactions mediated by [LCuNR₂], in which the neutral form of the catalyst, and not the cuprate, was determined to be more active.^{26,27}

The NHC ligand scaffold also lent itself well to the study of the fundamental chemistry of the related trifluoromethoxy group (OCF₃).²⁸ The OCF₃ group has been described as ‘the least well-understood’ fluorine-containing substituent, stemming from the fact that for a long time convenient OCF₃ salts were unavailable.²⁹ Such salts exist today,³⁰ and despite the fact that new stoichiometric methods to prepare trifluoromethyl ethers were starting to emerge at the time of our work,^{31–34} there was not a single report of a structurally characterized metal complex bearing the oxygen-bound ligand OCF₃.

The species ‘CuOCF₃’ was reported in the literature,³⁰ but we established that in the solid state, this existed as the ion pair [(MeCN)₄Cu][OCF₃].²⁸ In acetonitrile-*d*₈, ‘CuOCF₃’ exhibited a broad resonance band in the ¹⁹F NMR spectrum at the same chemical shift as the silver analogue ‘AgOCF₃’, suggesting that they also both exist as ion pairs in acetonitrile solutions.

We found, however, that when [(SIPr)CuCl] [SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene] was reacted with ‘AgOCF₃’, a sharp resonance appeared in the ¹⁹F NMR spectrum, suggesting the

formation of a more-static structure, such as **9** (Scheme 4).²⁸ The NHC-containing gold chloride derivative similarly produced complex **10**. The new species that were formed could be isolated and structurally characterized, which verified their connectivities and provided the first structural parameters of a metal complex bearing an OCF₃ ligand (Figure 1).²⁸



Scheme 4

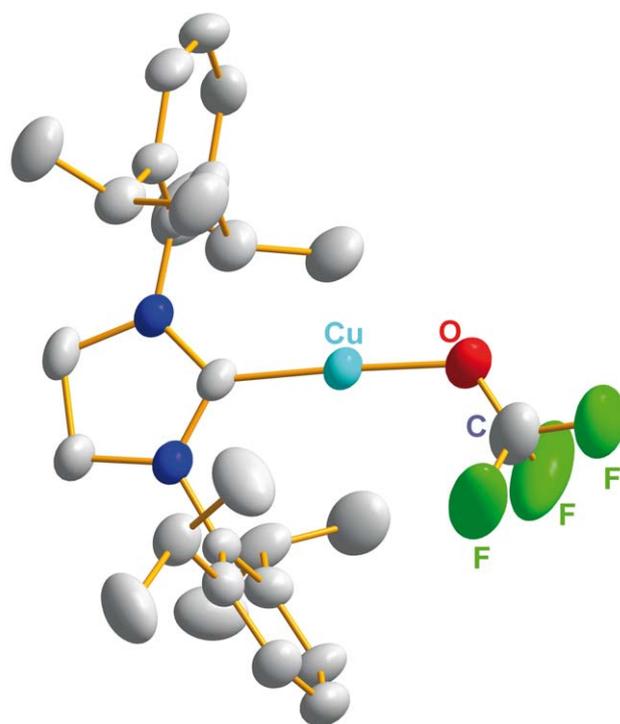
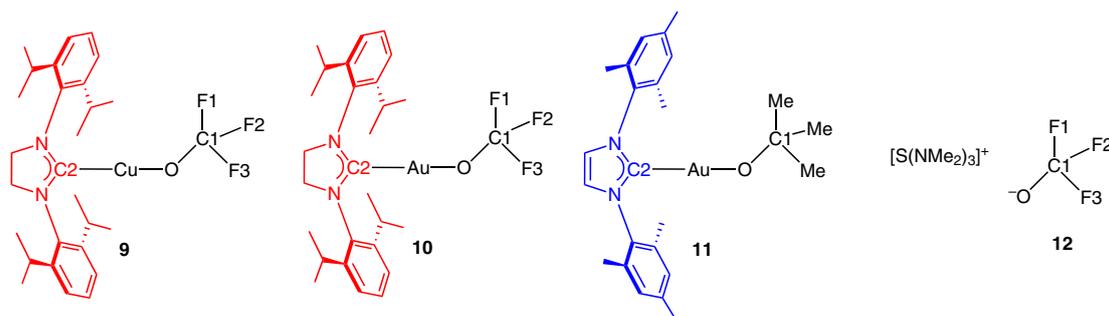


Figure 1 X-ray crystal structure of [(SIPr)Cu(OCF₃)] (**9**) (hydrogens are omitted for clarity)

The choice of ligand was key in isolating the trifluoromethoxy complexes, with SIPr being the only ligand tested that could prevent the decomposition of the generated [LM(OCF₃)] complex (M = metal) to [LMF] and carbonyl difluoride. It is possible that the bulky SIPr ligand in **9** and **10** prevents the M–O–C–1 bond angle from becoming small enough to enable β-fluoride eliminations. Interestingly, trifluoromethoxy complexes **9** and **10** displayed incredibly short carbon–oxygen bond lengths in comparison with that of the known *tert*-butoxide derivative **11**,¹⁸ but similar to that of organic salt **12**³⁵ (Table 2).

Table 2 Comparison of Bond Lengths (Å) and Angles (°) in Various Structures, including (Trifluoromethoxy)metal Complexes **9** and **10**

Bond length or angle	Complex 9	Complex 10	Complex 11	Complex 12
M–O	1.849(4)	2.058(4)	1.990(8)	–
M–C2	1.876(5)	1.978(5)	1.971(1)	–
O–C1	1.232(10)	1.247(7)	1.423(14)	1.227(4)
M–C1 (contact)	2.688(7)	2.868(6)	2.90(1)	–
M–O–C1	120.7(5)	118.2(4)	115.4(7)	–

In a qualitative model determined by the Natural Bond Orbital (NBO) program,³⁶ the carbon hybrid orbitals to fluorine atoms were all calculated to have more p-character ($sp^{3.31}$, $sp^{3.61}$, and $sp^{3.41}$), leaving more s-character to bond with the oxygen; the carbon hybrid orbital to oxygen was calculated as $sp^{2.05}$. Another interesting structural feature of complexes **9** and **10** was that they were found to exhibit short M–C1 contacts (Table 2), much shorter than the sum of the van der Waals radii of the metal and carbon.²⁸ More work is needed to determine whether or not there is any physical meaning in these short contacts or if they are just inherent in the structures or artifacts of crystallization. Nevertheless, there is now proof of concept that transition metals can support trifluoromethoxy ligands, and it will be interesting to see in the near future if such complexes can participate in the catalytic trifluoromethylations of organic substrates.

3 The Redox Chemistry of Copper– and Nickel–Fluoroalkyl Complexes

One of the original reasons we sought to prepare well-defined and isolable metal–perfluoroalkyl complexes was to investigate their electrochemical properties. First row metals, such as copper and nickel, often react through one-electron radical pathways. Therefore, understanding the redox properties of such perfluoroalkyl complexes should be important for methods development. Indeed, a recent study showed that aromatic perfluoroalkylations can be performed under electrocatalytic conditions.³⁷ We were surprised, however, that before our initial studies there was not a single report on the electrochemical properties of nickel– or copper–trifluoromethyl complexes in the literature.³⁸

Although a redox potential is just a measure of the absolute energy difference between the reduced and oxidized forms of a couple, qualitative evaluations can be made about trends in redox potentials stemming from substituent effects within a family of molecules.³⁹ In other words, when analyzing redox potentials within a family of molecules, emphasis should be placed on the relative, rather than the absolute, energy differences. When doing so, an assumption is made that the differences in solvation and ion pairing between the reduced and oxidized forms stay the same throughout the family. As long as there are no major structural changes occurring in the redox reaction, the trends should be informative and worth establishing.

We made a substantial effort to establish such trends in the electrochemical properties of metal–trifluoromethyl complexes.^{38,40–42} Figure 2 shows selected metal complexes from those studies whose redox potentials were determined by cyclic voltammetry. In all cases, we found that the oxidations of the metal–trifluoromethyl complexes occurred at more positive potentials than those of the related methyl complexes containing the same supporting ligand. Thus, the presence of the CF_3 group clearly and largely changes the *global* electronic properties of the parent nickel and copper nonfluorinated methyl derivatives.

In similar recent studies on organic molecules, Boltalina and co-workers found that perfluoroalkylated buckybowls were substantially more difficult to oxidize (and easier to reduce) electrochemically than their unsubstituted counterparts.^{43–45} Their group found that the addition of four perfluoroalkyl groups on a C_{70} fullerene ‘enhanced the electron accepting properties’ by 490 mV.⁴³

The CF_3 group has indeed been commonly described as an electron-accepting group in organic chemistry, and such a descriptor correlates in most cases with reactivity. For instance, competitive electrophilic aromatic substitution re-

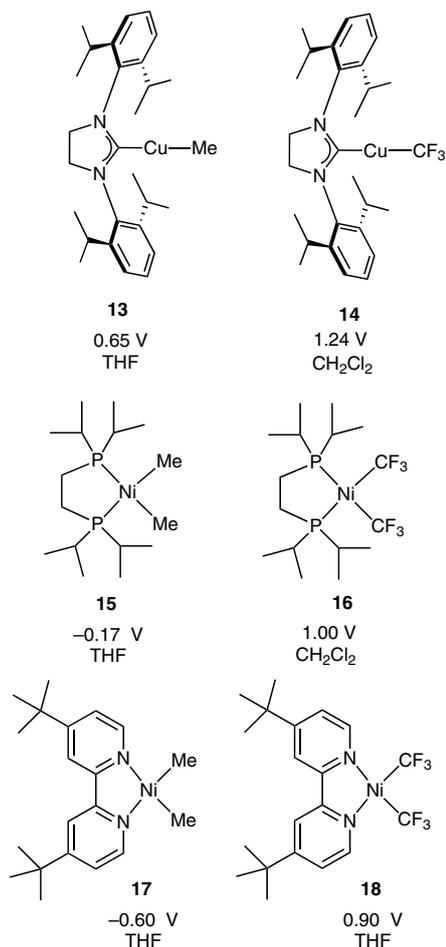


Figure 2 First oxidation potential for selected metal complexes (solvents indicated, values measured as the peak potential relative to Fc/Fc⁺)

actions of helium triton ions (He³H⁺) with (trifluoromethyl)benzene, benzene, and toluene provided the following relative rates for tritium incorporation: 0.45, 1.00, and 2.1,⁴⁶ respectively, consistent with the idea that a CF₃ group is electron withdrawing through inductive effects.⁴⁷

One group has commented⁴⁸ that ‘it is surprising’ that perfluoroalkyl groups are unambiguously viewed as having marked electron-withdrawing ability, but Fornies and co-workers responded that this assertion was ‘obviously conflicting, and that it can be concluded that additional factors other than those taken into account by [the authors] in their calculations might be operative.’^{49,50} Fornies and co-workers provided infrared data on [MCF₃(CO)] complexes that exhibit minimal back-bonding relative to [MCl(CO)] derivatives to support their own assignment of the CF₃ ligand in these carbonyl complexes as an electron-withdrawing group.^{49,50}

Further discussions, clarifications, and deeper insights into the subtleties of the electronic effects of a CF₃ ligand have recently appeared in the literature^{40,51–53} and are beyond the scope of this account. In the context of the electrochemical data reported by our group, however, it

should be obvious to the reader that the discussions relating to electronics are limited solely to global effects. Considerations of specific and absolute atomic features *within* a whole molecule are best probed by other techniques.

To better rationalize the observed electrochemical trends of the trifluoromethyl complexes, density functional theory (DFT) calculations were performed on truncated versions of complexes **17** and **18**.⁴⁰ As shown in Figure 3, the highest occupied molecular orbital (HOMO) of [(bpy)Ni(CF₃)₂] (bpy = 2,2'-bipyridine) is stabilized over 1 eV relative to the nonfluorinated derivative [(bpy)NiMe₂]. Qualitatively, one then normally expects,³⁹ for complexes of the same family, that it would be more difficult to oxidize the derivative that possesses the more-stable HOMO. In this regard, the DFT predictions are fully in line with the experimental results.

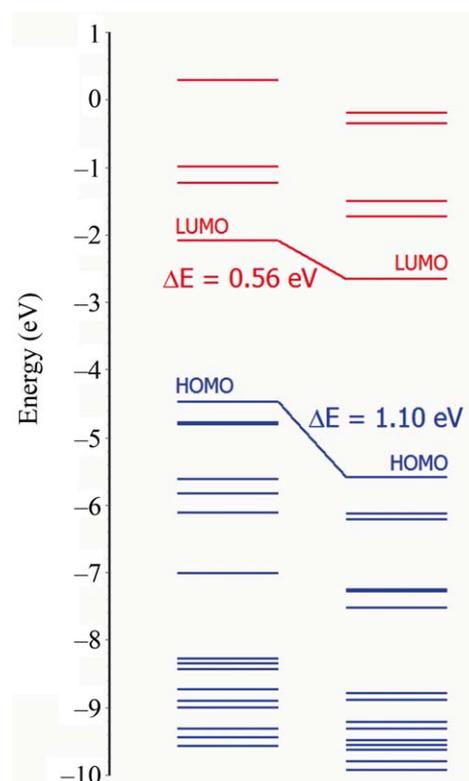


Figure 3 Calculated molecular orbital energy levels in the energy range -10.0–1.00 eV showing the occupied (blue) and unoccupied (red) molecular orbitals of [(bpy)Ni(CF₃)₂] (right) and [(bpy)NiMe₂] (left)

4 Nickel- and Copper-Mediated Trifluoromethylthiolations

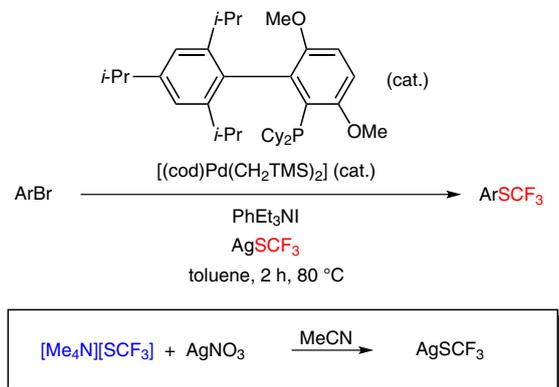
It was important to establish some of the basic science behind the nickel–bipyridine system described in this account because we also discovered that this metal–ligand combination was effective for the catalytic synthesis of aryl trifluoromethyl sulfides. The (trifluoromethyl)sulfanyl (SCF₃) group has become increasingly important in agrochemical and pharmaceutical fields.⁵⁴ The Hansch li-

Table 3 Hansch Lipophilicity Parameters for Selected Functional Groups

Nonfluorinated functional group	π -Value	Fluorinated functional group	π -Value
Me	0.56	CF ₃	0.88
OMe	-0.02	OCF ₃	1.04
SMe	0.61	SCF ₃	1.44

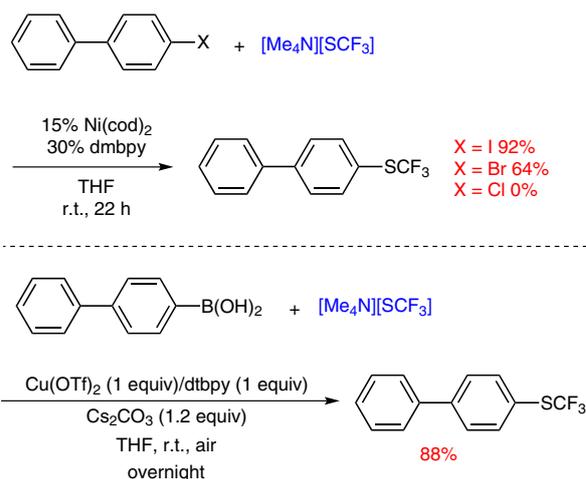
pophilicity parameter,⁵⁵ which is an estimate of the lipophilicity of a functional group, is large for SCF₃ (Table 3), which makes this moiety appealing for the design of new molecules capable of crossing lipid membranes.^{54,56}

In 2011, the state of the art in trifluoromethylthiolation methodology was the palladium-catalyzed reaction developed by Buchwald and co-workers shown in Scheme 5.⁵⁷ The reaction could convert a variety of aryl bromides into aryl trifluoromethyl sulfides at 80 °C, and it represented a major advance in metal-mediated trifluoromethylthiolations. However, stoichiometric use of the silver reagent AgSCF₃ was needed in this reaction, as was a full equivalent of a quaternary amine. We felt the combination of reagents for SCF₃ transfer could be made more economical, especially given the fact that the quaternary amine salt tetramethylammonium trifluoromethanethiolate ([Me₄N][SCF₃]) is used to make AgSCF₃ (Scheme 5).⁵⁸

**Scheme 5**

The [Me₄N][SCF₃] reagent is reasonably stable, and it is prepared by reacting elemental sulfur with TMSCF₃ and tetramethylammonium fluoride.⁵⁸ Despite reports that this reagent decomposes at 0 °C,⁵⁹ we found no evidence of decomposition when it was heated in dry THF at 60 °C. With a new assessment of its stability in mind, we screened different metals for cross-coupling activity at lower temperatures. We found that the 4,4'-dimethoxy-2,2'-bipyridine (dmbpy) ligand in combination with nickel could readily convert aryl iodides and bromides at *room temperature* into trifluoromethyl sulfides (e.g., Scheme 6).⁵⁶ However, the nickel system was unsuccessful for the trifluoromethylthiolation of aryl chlorides.

Aryl chlorides can be catalytically converted into arylboronic acids,⁶⁰ so we imagined that a workaround could involve a copper-catalyzed oxidative trifluoromethylthiolation reaction using arylboronic acids and [Me₄N][SCF₃] as the two nucleophilic coupling partners. This methodology indeed worked, and it was found that the reaction proceeds using 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) as a ligand in combination with copper(II) trifluoromethanesulfonate to give the catalyst and air as the oxidant (e.g., Scheme 6).⁶¹ In the same year, Qing and co-workers published a related copper-mediated oxidative coupling reaction using silver salts as oxidants.⁶²

**Scheme 6**

The combination of the nickel and copper protocols using the convenient [Me₄N][SCF₃] reagent ultimately provided access to a number of trifluoromethyl sulfides (Figure 4).^{56,61} Since these reports of trifluoromethylthiolations by our group, Weng et al. have shown that related well-defined and isolable [(trifluoromethyl)sulfanyl]copper complexes can be used as reagents for the nucleophilic trifluoromethylthiolation of aryl halides. They have provided evidence that the reactions proceed through Cu(I)/Cu(III) redox cycles.⁶³ Our group has structurally characterized a bis[(trifluoromethyl)sulfanyl]nickel complex,⁶⁴ but this well-defined compound did not show any SCF₃ transfer activity.

5 The Organometallic Chemistry of Nickel–Perfluoroalkyl Complexes

Whereas (trifluoromethyl)copper chemistry had a long standing history before our entry into the field, only a handful of experimental and theoretical studies on nickel–trifluoromethyl complexes were reported.^{65–73} Because nickel is perhaps the most-versatile metal for coupling nonfluorinated alkyl substrates,^{1,3,4,74–111} we were excited about exploring the chemistry of nickel–trifluoromethyl complexes and determining if these compounds could

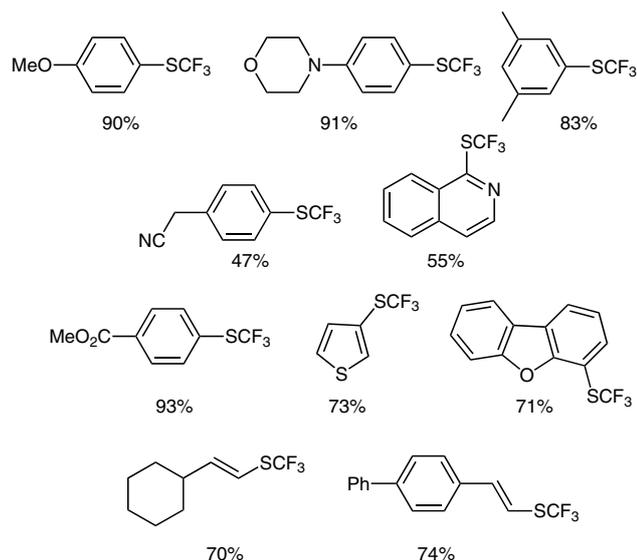


Figure 4 Yields of selected trifluoromethyl sulfides prepared using the convenient tetramethylammonium trifluoromethanethiolate reagent

also be coaxed into reactivity of interest to the synthetic chemist.

We first prepared a variety of $[(\text{dippe})\text{Ni}(\text{Ar})(\text{CF}_3)]$ complexes [$\text{dippe} = 1,2\text{-bis}(\text{diisopropylphosphino})\text{ethane}$, $\text{Ar} = \text{aryl}$] to explore their thermal stability.¹¹² The dippe ligand was chosen because the fragment $[(\text{dippe})\text{Ni}(0)]$ is well-known to both activate aryl halides at room temperature and reductively eliminate aryl and alkyl co-ligands.¹¹² Such reactivity is desirable for the studies of individual steps that are germane to cross-coupling catalysis. However, we found that efficient coupling of the Ar and CF_3 co-ligands in the new $[(\text{dippe})\text{Ni}(\text{Ar})(\text{CF}_3)]$ complexes did not take place. Although the nonfluorinated complexes $[(\text{dippe})\text{Ni}(\text{Ar})\text{Me}]$ readily eliminate methyl-

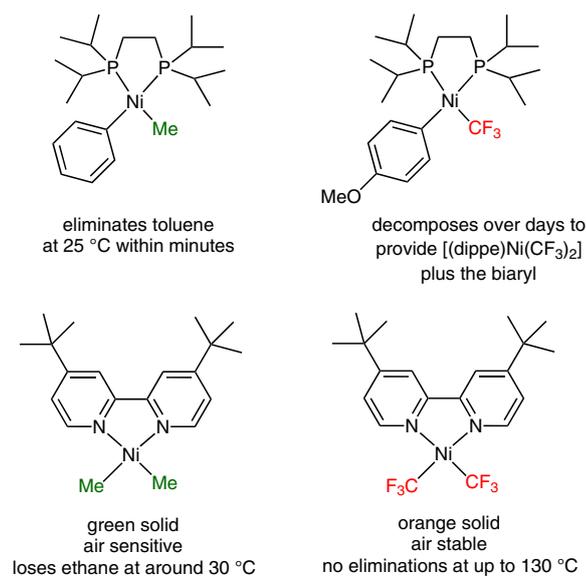


Figure 5 Basic reactivity patterns of selected nickel–methyl and –trifluoromethyl complexes

arenes, the $[(\text{dippe})\text{Ni}(\text{Ar})(\text{CF}_3)]$ complexes decomposed over days to provide only $[(\text{dippe})\text{Ni}(\text{CF}_3)_2]$ as the major fluorine-containing product (e.g., Figure 5).

Alkanes are known to be readily eliminated from $[(\text{bpy})\text{NiR}_2]$ derivatives, therefore related complexes of nickel were also explored for their ability to reductively eliminate organofluorines.⁴⁰ Despite displaying exceptionally distorted square-planar geometries in both the solid state and in the gas phase (e.g., Figure 6), the $[(\text{bpy})\text{Ni}(\text{R}_f)_2]$ ($\text{R}_f = \text{fluoroalkyl}$) complexes did not reductively eliminate a fluoroalkane coupled product upon heating (e.g., Figure 5).⁴⁰

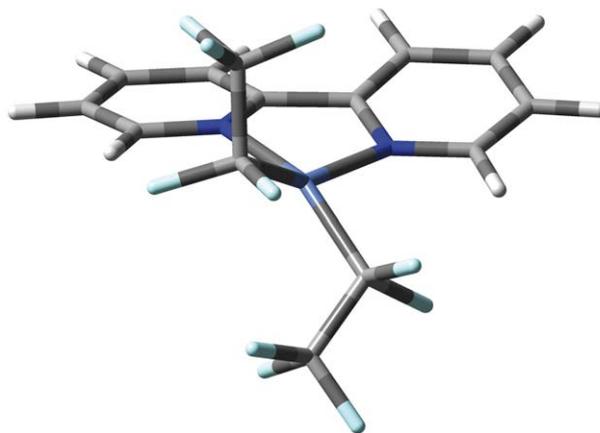
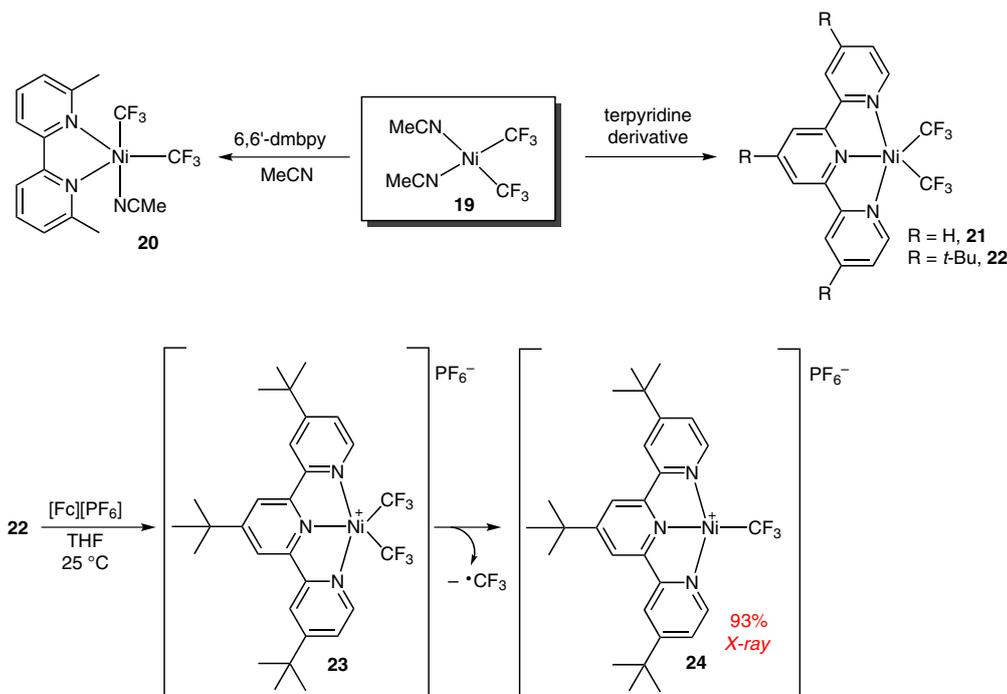


Figure 6 Optimized (m6-31g*) geometry of $[(\text{bpy})\text{Ni}(\text{C}_2\text{F}_5)_2]$

One of the characteristic features of the four-coordinate nickel(II)–trifluoromethyl complexes is that they are thermally robust with respect to the loss of CF_3 . While this feature lends itself well to fundamental studies, it also hampers catalysis development because reactions like reductive eliminations involving fluoroalkyl groups are so slow. The large stabilization of the HOMO that was seen upon fluorination of the nickel–bipyridine complexes (see Figure 3) brought two ideas to mind:

- (1) Destabilizing the HOMO within a family of complexes we had studied thus far would be necessary to render a metal complex capable of actually transferring one or both of its perfluoroalkyl groups.
- (2) Exploiting the HOMO stabilization that fluorine is well-known to provide might allow us to study fleeting intermediates in our terpyridine-based nickel alkylation chemistry.^{1,3,4,113}

We imagined that both of these ideas could be explored experimentally given the appropriate (fluoroalkyl)nickel precursor. Bis(acetonitrile)nickel complex **19** was found to be incredibly useful and gave us access to the remarkable 6,6'-dimethyl-2,2'-bipyridine (dmebpy) complex **20** (Scheme 7),⁴² whose reactivity we are currently comparing with the more-stable four-coordinate derivative **18** (see Figure 2). We have also been able to prepare the five-coordinate terpyridyl complexes **21** and **22**. The five-coordinate (fluoroalkyl)nickel complexes **20–22** are all



Scheme 7

noteworthy because nonfluorinated nickel(II)–alkyl species often decompose upon the formation of complexes whose coordination numbers are higher than four.⁴²

The quasi-stability of terpyridyl complex **22** permitted studies of its redox chemistry. One of the species we had hoped to learn more about was a terpyridylnickel(III) species bearing nickel–carbon bonds, as this species was the only putative intermediate of a proposed catalytic cycle that had yet to be fingerprinted.⁴² Moreover, nickel(III) intermediates had been implicated in the vast majority of proposed catalytic cycles involving nickel and alkyl radicals, yet it was difficult to obtain information on nickel(III) species bearing nickel–carbon bonds that are part of both the isolated alkyl or aryl group *and* a co-ligand relevant for contemporary alkyl cross-couplings.⁴² Reports of organonickel(III) complexes are known, but they involve nickel–carbon bonds that are either part of a supporting chelating pincer ligand^{114–119} or part of a system containing co-ligands that are not known/less active in contemporary cross-coupling reactions.^{120–123}

In bulk solution, **22** reacted with 1 equivalent of a ferrocenium salt to produce the putative nickel(III) intermediate **23** (Scheme 7). Upon workup, only nickel(II) complex **24** could be isolated, which presumably is formed by the reductive homolysis of transient complex **23** causing the loss of a CF_3 radical. Further support for both the generation of **23** and subsequent loss of CF_3 radicals came from spectroelectrochemical electron paramagnetic resonance studies in collaboration with Axel Klein from the University of Cologne.⁴²

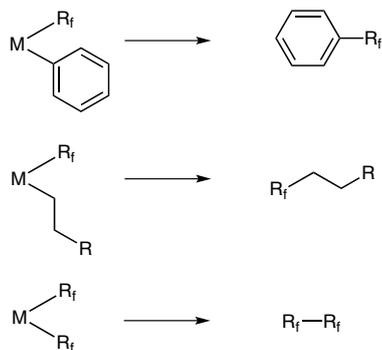
Our data on the terpyridine complexes provide a simple illustration that changing the coordination number and oxidation state of the nickel center can indeed lead to a more-

reactive trifluoromethyl complex. Indeed, loss of a CF_3 radical from **23** produced **24** in 93% isolated yield (Scheme 7). The onus remains in designing a system that can be rationally incorporated into a catalytic cycle of synthetic interest. We have recently shown, however, in collaboration with Yulia Budnikova,¹²⁴ that terpyridinenickel is an effective electrocatalyst for the fluoroalkylation of olefins.

6 Outlook

The use of base metals in catalysis is expected to grow as researchers learn to tame their reactivity. As discussed above and in other reviews,^{51,125} base metals have been incredibly important to the development of fluoroalkylation chemistry. The past five years have been particularly exciting as there has been an explosion of activity and progress in further developing the chemistry of copper in the field.^{125–158} Amii and co-workers published a landmark paper in 2009 on catalytically trifluoromethylating electron-poor aryl halides using copper,¹⁵² but the search for a copper catalyst that can display the same catalytic activity towards electron-rich aryl halides is still ongoing and no doubt hotly pursued.

Methods development using other first-row metals, such as nickel, to perform fluoroalkylations is still in its infancy, which we hope means there are lots of new and exciting reactions yet to discover. Understanding the fundamental organometallic chemistry shown in Scheme 8 using different metal–ligand combinations will surely continue to play a role in advancing the science.



Scheme 8

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